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SEPTICEMIA OF THE NEWBORN
A REVIEW OF THE CASES AT GRACE
NEW HAVEN COMMUNITY HOSPITAL
FROM 1957 - 1963

DONALD A. O'KIEFFE, JR.

1964

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SEPTICEMIA OF THE NEWBORN: A REVIEW
OF THE CASES AT GRACE NEW HAVEN
COMMUNITY HOSPITAL FROM 1957-1963

by

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A thesis presented to the faculty of the
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Department of Pediatrics
Yale University School of Medicine

1964

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INTRODUCTION

Neonatal sepsis with a high mortality rate continues to be a perplexing problem to the physician, despite a multitude of chemotherapeutic agents and major improvements in the management of pregnancy. The most important aspect of the problem is the early diagnosis of infection in the newborn. As yet there is no clear-cut early clinical syndrome which reliably indicates sepsis. Instead, the diagnosis most often is made on the basis of non-specific signs and clinical intuition.

The purpose of the present paper is to attempt through careful review of sixty-six cases of sepsis of the newborn, to present the earliest clinical signs of sepsis as well as other facts and figures. It is obvious that mortality will be decreased significantly only as the index of suspicion of sepsis increases and necessary cultures are drawn early and appropriate antibiotic treatment instituted. It is the hope of the author that the value of clinical information about the mother and delivery of the baby and certain signs observed in the neonatal course will help raise the index of suspicion that sepsis might be present.

In 1919 Ylppo (1) reported a careful bacteriological study of the blood and organs obtained postmortem from infants dying with a number of clinical diseases. In this series 12 of 29 heart blood cultures yielded growth; in 6 of these the micro-organism cultured was the colon bacillus. It was Ylppo's conclusion that post-mortem cultures of heart blood properly taken immediately after death, are reliable indicators of an ante-mortem blood stream invasion.

The concept of neonatal sepsis was first clearly described by Dunham in 1933 (2). Working at Yale, Dunham reviewed 39 cases of sepsis in which she found the majority of cases to be caused by *Streptococcus* and *Staphylococcus* (chart 1), and males to be affected three times as frequently as females. Of the 39 cases, symptoms were present at birth in 8; on the first day of life in 4; during the first week in 19 cases; during the second week in 9 and later than the second week in 8. Fever was present in 32 of the 39 cases and jaundice was absent in the cases of *Streptococcal* sepsis, but present in 7 of the 11 cases of *Staphylococcal* sepsis and 6 of 10 infections caused by *E. Coli*. Ten mothers were ill at the time of delivery of the infant or had febrile puerperium. Four mothers had septicemia, two - thrombophlebitis, one had "grippe" and one had pyelitis and nephritis which was fatal. Two mothers had unexplained fever during the puerperium. Seven mothers' membranes ruptured prematurely (5 of these children had *Staphylococcal* infections; one *Streptococcal* and 1 *B. Coli*). Two infants had infections following circumcision. In 28 cases of septicemia there was one source of infection and in 5 cases several sources. Of the 39 cases, thirty-four died. Two *B. Coli* and three *Staphylococcus* cases survived. Fifteen of the thirty-four who died, did so before the first week. Dunham concluded that in spite of the general impression to the contrary, septicemia is an important and relatively frequent cause of morbidity and mortality in the newborn. She urged that blood cultures be taken when an infant becomes ill and the diagnosis is obscure.

Silverman and Homan (3) published their review of 25 cases

CHART (1)

BACTERIOLOGIC FINDINGS

	1933 Dunham 39 cases	1949 Silverman & Homan 25 cases	1956 Smith & Good 15 cases	1957 Nyhan & Fousek 102 cases
STREPTOCOCCUS	15	4	-	29
E. COLI	10	14	9	34
STAPHYLOCOCCUS	11	4	3	12
KLEBSIELLA A.	-	1	-	-
PNEUMOCOCCUS	2	-	-	8
PROTEUS	-	1	-	-
SALMONELLA	-	1	-	-
PSEUDOMONAS	-	-	1	13
PARACOLON	-	-	1	-
MIXED	-	-	1	4
OTHER	-	-	-	6

CHART (2)

SUMMARY OF COMPARATIVE FINDINGS

	DUNHAM	SILVERMAN & HOMAN	SMITH & GOOD	NYHAN & FOUSEK
AGE OF ONSET (DAYS)	13.6	11.1	8.6	9.6
SEX - MALE/FEMALE	30/9	19/6	7/8	70/32
PREMATURE	8	4	3	43
<u>PRESENTED WITH:</u>				
TEMPERATURE	33	14	8	35
G.I. SYMPTOMS	8	9	5	22
JAUNDICE	9	11	2	20
SKIN LESIONS	18	4	1	23
RESPIRATORY DISTRESS	7	8	4	13
CNS SYMPTOMS	3	3	4	14
OMPHALITIS	7	0	1	2
<u>COURSE:</u>				
FEVER OVER 38.3 C.	24	8	10	-*
HEPATOMEGALY	5	9	10	49
ICTERUS	14	14	3	28
MENINGITIS	9	5	6	31
SKIN LESIONS	18	5	1	-
NEUROLOGIC SIGNS	-	3	4	-
ANEMIA	15	12	6	-
LEUKOCYTOSIS	13	17	8	24
LIVED	5	11	13	30
DIED (PER CENT)	34 (87%)	14 (56%)	2 (13%)	76 (71%)

* the (-) means not specifically mentioned.

in 1949. In their article, they proposed strict criteria for the selection of cases: "those cases were selected in which infection of the blood stream appeared to be the major affection. In addition the following were specifically omitted: 1) cases in which a simple or transient bacteremia accompanying a clear-cut major disease seemed likely (pneumonia, osteomyelitis, meningitis, etc.); 2) septicemia of late onset in the course of severe, chronic and debilitating illness (chronic diarrhea, various post-operative states); 3) solitary massive cutaneous infection followed by late onset of septicemia; 4) congenital anomaly of major significance with late onset of septicemia (omphalocele, atresia of the esophagus, etc.) and 5) cases of congenital syphilis with septicemia."

In their review they found that the majority of cases were caused by *E. Coli* (chart 1). In three cases there was maternal infection; four cases had a difficult delivery and four were premature. Elevation of temperature was noted in 16 cases and jaundice in 11. In terms of age of onset, 6 cases developed within the first two days; six from day 3-7; five from day 8-14 and eight from day 15-30. Nineteen of the twenty-five cases were males, and urine culture was positive in twelve cases. Sixteen cases were treated and fourteen of the twenty-five died.

They concluded that neither their series nor the collected published evidence afforded statistical proof of the efficacy or lack of efficacy of therapy in this syndrome. They felt, as Dunham, that the diagnosis should be suspected in every newborn who is obscurely ill. More specifically, the combination of

fever and jaundice in the newborn should be regarded as indicating sepsis until proven otherwise. They strongly urged early blood culture, umbilical stump culture, complete blood count, urinalysis, lumbar puncture and sedimentation rate be performed routinely on those infants suspected of having sepsis. Prompt and vigorous antibiotic therapy with combined agents should follow the work-up while waiting for cultural confirmation.

Smith and Good (4) in 1956 reported fifteen cases of neonatal sepsis at the University of Minnesota Hospital. For selection of their cases they used the criteria proposed by Silverman and Homan. Bacteriological study revealed a preponderance of infections caused by *E. Coli*. They found temperature elevation above 38.3 degrees C. in 8 cases and jaundice in 2. Of the fifteen cases, seven were male and three were premature. Three of the cases developed within the first 2 days; four cases from day 2-4; two cases from day 5-7; three cases from day 8-14 and three cases from day 14-30. Thirteen of the fifteen cases lived. They concluded much as the other investigators in the field that the onset of sepsis can be extremely subtle and often only manifested as a "failure to thrive". Prompt culturing of the blood, CSF, and urine is necessary and antibiotic therapy directed at the coliform and Staphylococci organisms immediately instituted. Also they felt that prophylactic antibiotic treatment against septicemia in the infant born after prolonged labor with early rupture of the membranes should be started - directed principally against the above-mentioned organisms.

In 1958, Nyhan and Fousek (5) reviewed the cases of neonatal

sepsis at Yale from 1933-1957, taking up where Dunham left off. The criteria for selection of cases were essentially those of Silverman and Homan. However, patients with pneumonia, meningitis, or osteomyelitis were not excluded unless these conditions clearly antedated clinical manifestations of septicemia. Over the 25 year period, 106 cases met the above criteria and the distribution of cases according to the invading organism is shown in chart (1). It is noteworthy that from 1933-1943, *B. Streptococcus* is the most commonly cultured organism whereas in the period 1944-1957, *E. Coli* emerges as the most frequent pathogen. Also *Pseudomonas* appears for the first time as a significant organism in neonatal sepsis in the 1944-1957 period. Fever, abdominal distention, icterus and hepatomegaly were the most common clinical manifestations suggesting sepsis (chart 2). However, in most patients the clinical picture was one of general, rather vague systemic illness. Of the 106 cases, 76 died, yielding a mortality of 71%.

The incidence of death due to neonatal sepsis is extremely difficult to evaluate. The incidence rises when complete post-mortem studies are performed on all infants who die. Since few hospitals perform complete post-mortem examinations on all infants who die, the vital statistics in this regard is probably low. For example, in 1955, 27% of the 77,351 deaths which occurred in the first 28 days of life were attributed to "immaturity unqualified" and less than 6% of the deaths were attributed to infection. In contrast, post-mortem studies from various sources have revealed an incidence of infection as a cause of neonatal

death, ranging from 10-15% (6). Inadequate bacteriological studies and tissue preparations and the difficulty in detecting the subtle gross changes which occur in sepsis are the main problems involved in accurate diagnosis. Also the frequency with which antemortem blood cultures are drawn varies significantly from institution to institution and this necessarily means that the frequency with which the antemortem diagnosis is made will likewise vary. An additional factor which confuses the interpretation of statistics is the role which drug toxicity plays in the mortality of these infants. As of yet there have been no studies which have shed any light on this aspect of the problem, but there probably have been a significant number of iatrogenic deaths which have been recorded as septic deaths.

PATIENT MATERIAL

Clinical records were reviewed of all infants under 30 days of age admitted to the Pediatric or Newborn Service of the Grace New Haven Community Hospital from July, 1957 to July, 1963 from whom positive blood cultures were obtained. The only cases which were specifically excluded were those in which the infection was secondary to an operation, aspiration or some manipulative procedure such as heart catheterization. It was deemed important to include all cases of sepsis even though they presented as meningitis, with congenital anomalies or as a pneumonia. A chart tabulating the presenting signs, including meningitis and congenital anomalies is presented. No case of osteomyelitis or significant skin infection occurred during this time period.

Blood cultures were managed as follows: they were drawn

observing strict aseptic technique. Three to five cc. of blood was divided between two bottles: one containing thioglycolate broth and the other trypticase soy broth. The bottles were then incubated at 37 degrees C. and checked at 24 hours. If positive or suggestive at this time, smears and subculturing was performed. All blood cultures were held five to ten days before being discarded as negative. Those cases were excluded in which there was growth in only one bottle or growth of a common contaminant and the clinical course also did not justify the diagnosis of sepsis.

During the six year period, sixty-six infants were found eligible for this study.

RESULTS

BACTERIOLOGICAL FINDINGS (CHARTS 3 & 4)

The organism most frequently cultured was E. Coli. It was responsible for twenty-seven cases of sepsis or 41% of all infections, an incidence similar to that found by Nyhan and Fousek in the 1944-1957 period. Noting the occurrence of E. Coli infections in the first three years of this survey as compared with the second three year period (chart 10), one is impressed with the substantially large increase in cases in the second three year period (from eight cases in the 1957-1960 period to nineteen cases in the 1960-1963 period). Other investigators previously have noted that this organism is on the rise as an etiological agent of neonatal sepsis, a contention supported by this survey.

CHART (3)

BACTERIOLOGICAL FINDINGS

CULTURED ALSO FROM:

ORGANISM	INCIDENCE	%	MIXED	CSF	URINE	SKIN	CORD	N&T	POST-MORTEM*
E. COLI	27	41	2**	5	4	1	1	4	11-9-9-7
ENTEROCOCCI	12	18	0	5	0	0	0	1	9-8-7-3
STAPHYLOCOCCUS AUREUS	3	4.5	0	0	0	0	1	1	2-2-0-0
PSEUDOMONAS AERUGINOSA	11	16.5	1***	0	0	0	2	0	8-7-6-6
KLEBSIELLA AEROBACTER	6	9	1***	1	0	0	0	0	5-4-4-3
PARACOLON	2	3	0	0	0	0	1	0	1-1-1-0
B. ALKALESCENS	1	1.5	0	0	0	0	0	0	0-0-0-0
H. INFLUENZA type B	1	1.5	0	1	0	0	0	0	1-1-1-0
PNEUMOCOCCUS type 8	1	1.5	0	0	0	0	0	0	0-0-0-0
PROTEUS MIRABILIS	1	1.5	0	0	0	0	0	0	0-0-0-0
B. ANTITRATUM	1	1.5	0	0	0	0	0	0	1-1-0-0
total cases	66	99.5%							

* figure 1: deaths; 2, autopsies; 3, cultured at autopsy; 4, positive cult.

** 1) E. Coli and B. Subtilis and 2) E. Coli and Staph Citreus

*** Klebsiella Aerobacter and Pseudomonas Aeruginosa

ETIOLOGY 1933 - 1963

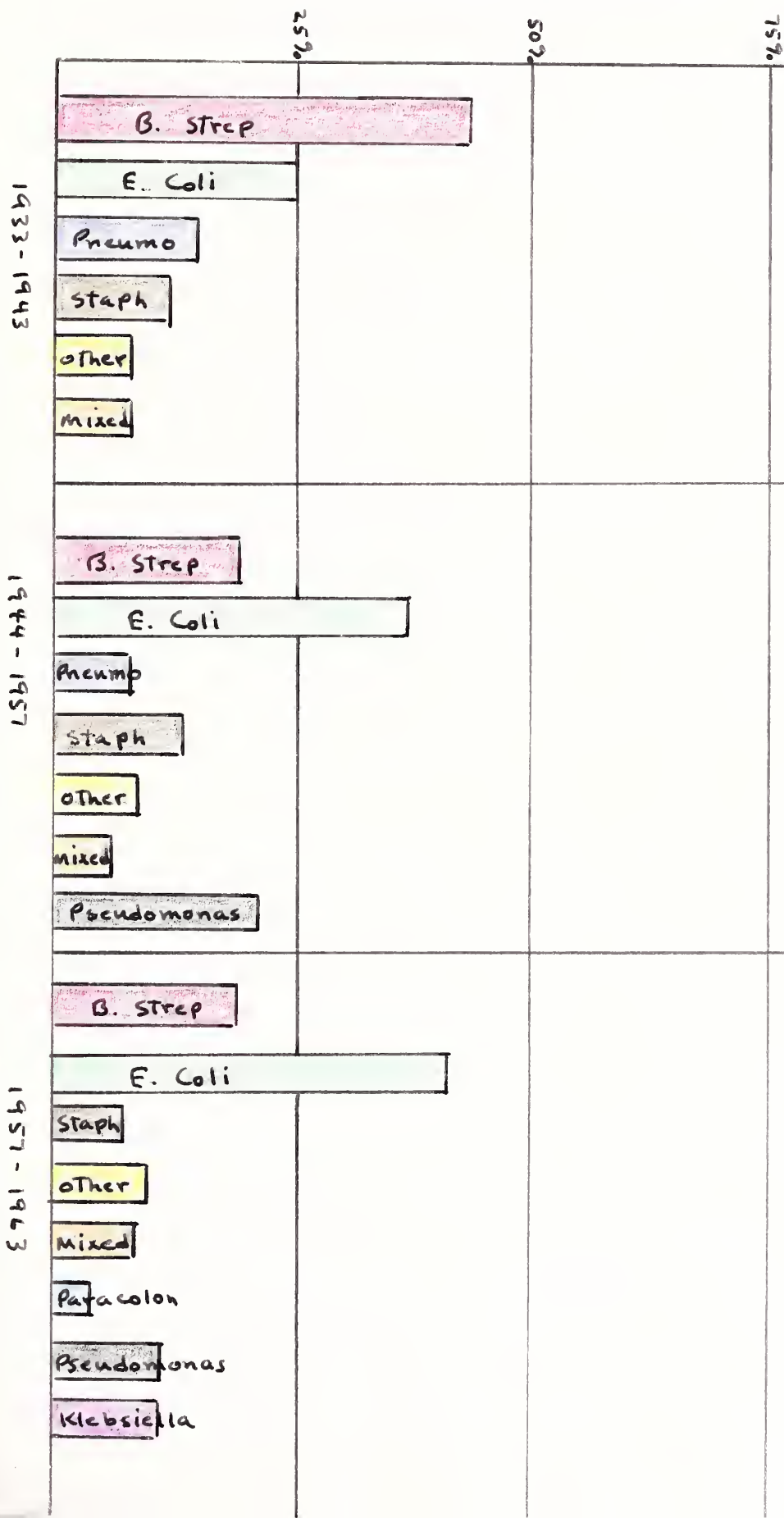


CHART (5)

GENERAL INFORMATION ABOUT THE PREGNANCY

	E. COLI	ENTEROCOCCUS	PSEUDOMONAS	STAPHYLOCOCCUS	KLEBSIELLA	PARACOLON	B. ALKALESCENS	H. INFLUENZA	PNEUMOCOCCUS	PROTEUS	B. ANTITRATUM	total
AGE OF MOTHER: UNDER 22	4	4	4	1	1	0		1	0	1	0	16
22 - 30	14	4	5	2	1	1		0	0	0	1	28
OVER 30	4	2	1	0	3	0		0	1	0	0	11
RACE: WHITE	27	8	9	2	5	1	1	1	1	1	1	57
DIABETES	0	0	0	1	0	0	0	0	0	0	0	1
INFECTIONS WITH TEMP. LAST WEEK OF PREG.	3	1	2	0	1	1	0	0	1	0	0	9
BLEEDING LAST TRIMESTER	2	0	3	0	2	0	0	0	0	0	0	7
PREMATURE RUPT OF MEMBRANES (24 HOURS)	3	2	1	0	1	0	0	0	0	0	0	7
DIFFICULT DELIVERY*	4	0	1	0	1	0	0	1	0	0	0	7
PLACENTA PRAEVIA	1	0	0	1	0	0	0	0	0	0	0	2
ABRUPTIO PLACENTA	1	0	0	0	0	0	0	0	0	0	1	2
BREECH DELIVERY	1	1	3	0	0	0	0	0	0	0	1	6
C-SECTION	0	0	0	2	1	0	0	0	0	0	0	3

* i.e. 2nd stage labor over 15 hours, prolapsed cord, trauma, dystocia, etc.

CHART (6)

GENERAL INFORMATION ABOUT THE BABY

	E. COLI	ENTEROCOCCUS*	PSEUDOMONAS	STAPHYLOCOCCUS	KLEBSIELLA	PARACOLON	B. ALKALESCENS	H. INFLUENZA	PNEUMOCOCCUS	PROTEUS	B. ANTI TRATUM	total
PREMATURE	15	4	8	2	3	1	0	0	0	0	1	34
APGAR UNDER 6 AT 1 MIN.	6	2	4	2								14
UNDER 6 AT 5 MIN.	3	2	2	2								9
WBC (MAXIMUM) UNDER 10,000	4	2	1	0	0	0	0	1	0	0		8
OVER 10,000	15	2	1	1	2	1	1	0	0	1		24
HEMAGLOBIN: UNDER 15 mgm%	8	5	0	2	0	1	0			0		16
OVER 15 mgm%	13	2	3	1	2	0	1			1		23
BREAST FED	5	0	0	0	1	0	0	0	0	0	0	6
AGE OF ONSET 0 - 2	12	6	6	1	4	1	1	1	1	0	1	34
(DAYS) 3 - 7	10	2	3	0	1	1	0	0	0	1	0	18
8 - 14	4	2	2	2	0	0	0	0	0	0	0	10
15 - 30	1	2	0	0	1	0	0	0	0	0	0	4
MALE	20	5	8	2	3	1	1	1	0	1	1	43
CIRCUMCISION BEFORE ONSET	3	1	0	0	1	1	0	0	0	1	0	7

* three of twelve died within five hours of birth

CHART (7)

PRESENTED AS:

ORGANISM	NO SYMPT	DOING POORLY	PREMA- TURITY	JAUND	RESP DIST	MENIN- GITIS	G.I. SYMPT	CONG ANOM	FEVER	INF*
E. COLI	1	9	11	8	6	2	0	2	4	1
ENTERO- COCCUS	0	1	2	2	4	4	0	1	1	0
STAPH	0	1	1	0	2	0	1	0	0	0
PSEUDO- MONAS	0	4	10	4	7	3	0	1	0	0
KLEBSIELLA AEROBACTER	0	2	1	1	0	0	0	2	1	0
PARACOLON	0	1	1	0	1	0	0	0	1	0
B. ALKA- LESCENS	0	0	0	0	0	1	0	0	0	0
H. INFLUENZA	0	1	0	0	0	0	0	0	0	0
PNEUMOCOCCUS	1	0	0	0	0	0	0	0	0	0
PROTEUS	0	0	0	1	0	0	0	0	1	0
B. ANTITRA- TUM	0	0	1**	0	0	0	0	0	0	0
total	2	19	27	16	20	10	1	6	8	1

* i.e rash or omphalitis

** immature

CHART (8)

SUBSEQUENT FINDINGS AND COURSE

	E. COLI	ENTEROCOCCUS [*]	PSEUDOMONAS	STAPHYLOCOCCUS	KIEBSIELLA	PARACOLON	B. ALKALESCENS	H. INFLUENZA	PNEUMOCOCCUS	PROTEUS	B. ANTITRATUM	total
SEVERELY ILL	19	9	7	2	4	1	0	1	0	0	1	44
ICTERUS	16	3	6	2	2	0	0	1	0	1	0	31
HEPATOMEGALY	16	5	2	2	2	1	1	1	0	1	0	31
TEMP. ABOVE 38.3 C.	8	4	2	0	3	1	0	1	0	0	0	19
ABD. DISTENTION	5	2	2	1	3	0	0	1	0	0	0	14
RESP. DISTRESS	8	3	7	1	3	1	0	1	0	0	1	25
SPLENOMEGALY	3	2	0	0	0	0	1	1	0	0	0	7
MENINGEAL SIGNS	5	3	1	0	0	0	0	1	0	0	0	10
CYANOSIS	6	4	4	0	3	1	0	0	0	0	0	18
SKIN LESIONS	4	1	0	0	0	1	0	1	0	1	0	8
LETHARGY	12	4	5	2	4	1	0	0	0	0	0	28
APNEA	12	3	7	2	4	1	0	1	0	0	0	30
REGURGITATION	10	2	3	2	3	1	0	0	0	1	0	22
POOR FEEDING	18	7	5	2	3	2	0	1	1	0	0	39
RESTLESSNESS	8	7	2	0	2	0	0	0	0	0	0	19
IRRITABILITY	8	7	2	1	2	0	0	0	0	0	0	20

* three of the twelve patients died within five hours of age.

CHART (9)

LENGTH OF DOWNHILL COURSE AND TIME
ON DRUGS OF THOSE INFANTS WHO DIED

ORGANISM	LENGTH OF COURSE (DAYS)			DAYS ON ANTIBIOTICS			
	UNDER 1 DAY	2-4 DAYS	OVER 5 DAYS	NONE	1 DAY	2-4 DAYS	OVER 5 DAYS
E. COLI	0	9	1	2	3	5	0
ENTEROCOCCUS	3	6	0	2	3	4	0
STAPHYLOCOCCUS	0	1	1	1	0	0	1
PSEUDOMONAS	1	4	2	0	2	3	2
KLEBSIELLA	2	1	2	1	2	0	2
PARACOLON	0	1	0	0	0	1	0
H. INFLUENZA	1	0	0	0	1	0	0
B. ANTI TRATUM	1	0	0	0	0	0	0

CHART (10)

YEARLY BREAKDOWN FROM 1960

	<u>E. COLI</u>				<u>PSEUDOMONAS</u>				<u>ENTEROCOCCUS</u>				<u>KLEB. AEROBACTER</u>			
YEAR	60	61	62	63*	60	61	62	63	60	61	62	63	60	61	62	63
# OF CASES	6	6	5	3	2	4	3	0	2	1	2	0	2	1	0	2
AGE ONSET																
0 - 2 (DAYS)	2	4	2	3	2	1	3		2	1	0		2	0		1
2 - 7	4	2	1	0	0	2	0		0	0	1		0	1		0
7 - 14	0	0	2	0	0	1	0		0	0	1		0	0		0
over 14	0	0	0	0	0	0	0		0	0	0		0	0		1
COURSE																
0 - 2 (DAYS)	2	1	1	0	0	0	1		0	0	2		2	0		0
2 - 5	1	4	1	0	1	3	0		2	0	0		0	1		1
5 - 10	1	0	0	1	1	1	1		0	0	0		0	0		0
over 10	2	1	3	2	0	0	1		0	1	0		0	0		1
DIED	3	4	1	0	2	2	1		2	0	2		2	1		1

	<u>STAPHYLOCOCCUS</u>				<u>PNEUMOCOCCUS</u>				<u>H. INFLUENZA</u>			
YEAR	60	61	62	63	60	61	62	63	60	61	62	63
# OF CASES	2	0	0	0	0	0	0	1	0	0	0	1
AGE ONSET												
0 - 2 (DAYS)	1						1				1	
2 - 7	0						0				0	
7 - 14	0						0				0	
over 14	1						0				0	
COURSE												
0 - 2 (DAYS)	2						0				1	
2 - 5	0						1				0	
5 - 10	0						0				0	
over 10	0						0				0	
DIED	2						0				1	

* only cases occurring during first six months of 1963 are included.

CHART (11)

BREAKDOWN OF ETIOLOGY AND MORTALITY 1957-1963

JULY 1957 - OCTOBER 1960 NOVEMBER 1960 - JULY 1963

ORGANISM	# cases	deaths	% deaths	# cases	deaths	% deaths
E. COLI	8	3	37	19	8	42
PSEUDOMONAS	4	4	100	7	3	43
ENTEROCOCCUS	7	5	71	5	4	80
KLEBSIELLA	3	3	100	3	2	66
STAPHYLOCOCCUS	3	2	66	0	-	-
PARACOLON	2	1	50	0	-	-
PROTEUS	1	0	0	0	-	-
PNEUMOCOCCUS	0	-	-	1	0	0
B. ALKALESCENS	1	0	0	0	-	-
B. ANTITRATUM	1	1	100	0	-	-
H. INFLUENZA	0	-	-	1	1	100
	<hr/>	<hr/>	<hr/>	<hr/>	<hr/>	<hr/>
totals	30	19	63	36	18	50

overall % mortality for the 1957-1963 period 56%

Enterococcus was the next most frequent offender, responsible for twelve cases or 18% of all infections, approximately the same frequency found for B. strep in the 1944-1957 period. There was little change in the frequency with which Enterococcus was cultured between the two three-year periods of this review. Klebsiella-aerobacter infections occurred for the first time in Grace New Haven Hospital neonatal statistics, being responsible for six cases, and with the additional finding of eleven cases caused by Pseudomonas aeruginosa, the gram negative organisms are now by far the most important organisms causing sepsis.

THE PREGNANCY (CHART 5)

The age of the mother seems to have no significant bearing on the incidence of sepsis. As expected, the majority of cases occurred in the 22-30 age group. The incidence of sepsis was higher in the white race by a 6:1 ratio. However, this is approximately the same ratio as the overall white to negro birth-rate for this same period of time, so that it would appear that there is no significant difference between the races in regards incidence of sepsis.

Only one mother had diabetes and there were no other chronic systemic illnesses among the rest. Nine mothers had infections with elevated temperatures during the last week of pregnancy. Seven mothers were noted to have bleeding during their last trimester and seven had prematurely ruptured membranes 24 hours or more prior to delivery. "Difficult delivery", a concept encompassing complications such as a prolonged second stage of labor, prolapsed

cord, birth trauma and dystocia, occurred in seven cases. There were two cases of abruptio placenta and two cases of placenta praevia. Breech delivery was the method of delivery in six cases and Cesarean-section in three.

GENERAL INFORMATION ABOUT THE BABY (CHART 6)

One of the more important figures in this chart is the number of premature births. Thirty-four or approximately half of the infants in the review were premature. Fourteen infants had "APGAR scores" less than six at one minute and of those, nine still had apgar scores less than six at five minutes. In all, eleven of the fourteen died, including seven of the nine with the low apgar scores at five minutes. It would thus appear that an Apgar score less than six reliably indicates a poor prognosis.

Of the laboratory studies, thirty-two infants had WBC determinations. Twenty-four of these showed a leukocytosis over 10,000/cm³. Sixteen of thirty-nine infants with hemaglobin determinations had values less than 15 mgm%. However, unless serial hemaglobin determinations are done an anemia might be missed.

Six infants were breast fed prior to the onset of their sepsis, but in only one instance was the mother noted to have fever during that period.

The age of onset of infection is predominately within the first week (i.e. 52 of the 66 cases) and, more importantly, half of the cases had their onset within the first two days of life. This finding is in marked contrast to the finding of Dunham and other early investigators who found the average age of onset to be over

ten days (chart 2).

This study confirms the finding of other investigators that the incidence of sepsis is higher in males than in females by approximately a 2:1 ratio, although the distribution of offending organisms is fairly uniform between the sexes.

Circumcision preceding the onset of sepsis was performed in seven cases and in two cases clearly seemed implicated as the primary source of infection.

PRESENTED AS (CHART 7)

There were several frequently recurring associated findings and signs among the infants with sepsis. The most common occurred in twenty-seven infants who were prematurely born. Respiratory distress (20 cases) and "doing poorly" (19 cases) were next most frequently associated with sepsis as the first manifestations. Sixteen cases presented with jaundice as the initial sign, with meningitis and fever next in order of frequency. Congenital anomalies were seen in six cases. Two were entirely asymptomatic at the time of blood culture and there was one case each presenting with G.I. symptoms and skin infection.

SUBSEQUENT FINDINGS AND COURSE (CHART 8)

"Severely ill" was the term describing those infants considered by all observers to have a downhill course. Forty-four infants were noted to be severely ill during their hospital course and there seems to be no significant differences associated with the various pathogens. Thirty-one infants were noted to be jaundiced and a like number were noted to have hepatomegaly, most frequently

associated with an infection with E. Coli. Temperatures above 38.3 degrees C. were noted in nineteen cases. Of these nineteen cases, temperatures were elevated as early as the second day of life in five cases and on the third day of life in three others. Eight infants showed fever beyond the first week of life. In two cases temperatures were subnormal.

Abdominal distention was noted in fourteen cases and respiratory distress in twenty-five cases. It is of interest that of the eleven cases of infection with Pseudomonas, seven of these suffered with respiratory distress (however, eight of the eleven infants were premature). Cyanosis was found to be present in eighteen cases, meningeal signs in ten and splenomegaly in seven. Skin lesions were present in eight cases with no predominant causative organism.

In an attempt to substantiate the impression of several investigators that there are recognizable early clinical signs which strongly suggest sepsis, the following signs were tabulated. This information for the most part came from nurses' notes where in most instances these observations were the only ones recorded and frequently were the earliest mentioned if also recorded by other than nurse observers. Lethargy was noted to be present before cultures were drawn in twenty-eight cases; poor feeding in thirty-nine cases; irritability in twenty-one and restlessness in nineteen. Apneic episodes occurred during the course of illness in thirty cases and by and large were signs of a poor prognosis.

LENGTH OF DOWNHILL COURSE AND
TIME ON DRUGS OF THOSE INFANTS
WHO DIED (CHART 9)

An attempt was made to evaluate any effect of antibiotics on the course of those infants who died. In eight cases the downhill course (or, effectively, the length of the illness) was less than one day. These infants received no antibiotics or only an abbreviated course. The majority of those who died (22 infants) had courses of illness ranging from 2-4 days. Nine of these received antibiotics for one day and thirteen received a 2-4 day course of antibiotics. Six patients survived more than five days and five of these patients received antibiotics for the full five days or longer. Of these five, three had congenital anomalies while the other two were premature.

YEARLY BREAKDOWN FROM 1960 (CHART 10)

A closer analysis of the cases over the past three and one half years reveals that with the exception of *Staphylococcus* there does not appear to be a significant change in the incidence of cases of sepsis among the various pathogens. Also the age of onset of sepsis seems to be fairly constant - the majority of cases being detected during the first week of life. The "course" reflects mortality, for those cases who survive the acute stage of the illness will go on to have a longer hospital stay. The mortality rate seems to decrease appreciably between 1961 and 1962, especially noticeable in those cases caused by gram negative organisms (particularly *E. Coli*). However, *Enterococcus* does not seem to reflect this change.

OVERALL MORTALITY (CHART II)

The cases were separated into two periods: one from 1957-1960 and the other from 1960-1963. The mortality rate decreases from 63% in the earlier period to 50% in the later period. However, if the mortality attributable to Staphylococcal infection in the first period is eliminated, then the mortality rates between the two periods are comparable. Enterococcus, Klebsiella and Pseudomonas in that order seem to offer the poorest prognosis of the more frequent pathogens. The mortality rate for the whole six year period was 56% which is similar to that found by Silverman and Homan and somewhat lower than that reported by Nyhan and Fousek (72% mortality).

DISCUSSION

A review of sixty-six cases of neonatal sepsis during the period 1957-1963 has shown that gram negative organisms (especially E. Coli) are responsible for the large majority of infections. This supports the findings of Nyhan and Fousek and others that the etiological organisms more and more frequently are gram negative. The probable reasons for this trend will be discussed later. However, it is significant and should be mentioned here that all three cases of infection due to Staphylococcus in this review occurred in the 1957-1960 period, prior to the institution of a rigid program of antiseptic skin and cord care of the newborn with hexachlorophene baths (7). In the past, this gram positive organism had accounted for a significant number of cases of sepsis in every review.

As nursery conditions and practices become more aseptic, attention regarding initial exposure to the offending pathogen is turning toward intra-uterine life and the birth process. In the present study, it appears that complications of pregnancy and delivery are implicated in a significant number of cases as possible etiologic explanations for the ensuing neonatal sepsis in those involved infants.

Half of the infants acquiring sepsis in this study were premature, the majority of cases presenting as "prematurity" with "respiratory distress" and "doing poorly" the next most frequent initial manifestations of sepsis. This means that the physician particularly must be on his guard with premature infants and suspect sepsis at the slightest indication. "Doing poorly", respiratory distress and jaundice are sufficient reasons for drawing blood cultures.

Certain features of the subsequent course, findings and signs of sepsis were notable. In this review, the WBC seems to correlate fairly well with infection while anemia seems to be a less good indicator of sepsis in the complete evaluation of the infant. The temperature was elevated above 38.3 degrees C. in five of nineteen cases as early as the second day of life. This would support the value of taking temperatures at regular intervals routinely on newborn infants. As other investigators have pointed out, hepatomegaly and jaundice are important findings in sepsis of the newborn. In an attempt to specify certain clinical features of sepsis, the following signs were specifically looked for in the charts: lethargy, apnea, regurgitation, poor feeding, rest-

lessness and irritability. The high frequency of their occurrence indicates that fairly reliable clinical signs appear early in sepsis and should be looked for by nursing personnel and physicians. Of the above signs, apnea seems to correlate best with poor prognosis.

The effect of antibiotics on the course of sepsis is somewhat difficult to evaluate. There is little doubt that improvements in the prognosis of sepsis in the past and those to come in the future will center around antibiotic therapy. Little is known about the metabolism of drugs in the infant or the optimum dose needed of many drugs. In the past, drug toxicity has accounted for some deaths attributed to sepsis. In this review, of those infants who died, only six had hospital courses beyond five days. Five of these received antibiotics for longer than five days, and of these five, three had congenital anomalies and the other two were premature. In other words these were cases which were probably unresponsive to antibiotics because of other factors. The majority of deaths occurred in infants whose course was from 2-4 days and in whom adequate trial of antibiotics was not possible. This group, whose course most likely represents the natural course of the disease, would seem responsive to antibiotics if given early enough and maintained for a critical minimal length of time (about four days). The cases whose clinical courses were one day or less represent for the most part infants so severely infected either by the time of birth or arrival at the hospital that they cannot reasonably be expected to have been saved.

As regards mortality, there appears to be a significant improvement in the statistics; however, as mentioned in the

introduction, these statistics are subject to many variables some of which are only partly understood.

It is obvious that the entire clinical picture of neonatal sepsis has undergone a considerable change. On the one hand we have the fact of changing organisms and on the other we have the fact of earlier onset (or discovery) of sepsis. In regard to the latter aspect of the problem, it is probably accurate to say that a higher index of suspicion of sepsis, earlier and more frequent blood cultures and improved lab facilities have led to the discovery of many cases which in the past would not have been diagnosed and whose deaths might have been attributed to prematurity or other causes. The classical late-onset cases of the past are being eliminated now by more aseptic nursery conditions, more education of mothers and quicker and better treatment of pneumonias and other infections. Reducing this group of late-onset, or post-natal sepsis, has left us with the early-onset group as the most important group of cases. The bulk of this group probably reflects antenatal causes for sepsis. These are infants born prematurely or of septic mothers or after difficult deliveries. This is the group who either because of prematurity are unable to handle infections or, if full term, because of intra-uterine anoxia or other physiological disturbances may have their resistance decreased and are more susceptible when exposed to organisms.

The problem of changing organisms is not entirely separate from that posed by the changing age of onset of infection. The late-onset sepsis, or nursery-incurred infection, characteristically is a gram positive sepsis. Improvements in care and aseptic

conditions in the nursery have led to a decreased incidence of these cases and consequently are partly responsible for the change in proportion of gram positive to gram negative infections. In addition, the detection of previously missed early-onset sepsis adds numerically to the number of cases due to gram negative bacteria as most of these infections are caused by gram negative organisms, especially E. Coli. One possible explanation for this is the recently discovered high incidence of asymptomatic bacteriuria in pregnant women (8). Given a susceptible infant - either premature or a full term infant who has suffered anoxia or other intra-uterine embarrassment, a perfect situation exists for infection by any organism which invades his orifices or blood or contaminates the amniotic fluid. Whether anoxia makes the placenta permeable to bacteria; whether a minimal infection of the amniotic fluid occurs during labor or whether the infant is infected during birth is presently impossible to say, but in all probability these infants are infected by the time they are born and the original source of this infection may well be the urine of the mother.

The outlook for sepsis in the newborn must appear brighter. Earlier diagnosis, new improved antibiotics in clinically-determined optimal doses (especially for gram negative organisms), intra-theal antibiotics, the use of hypothermia and better post-natal care are factors which together should play a part in decreasing the mortality of this disease.

CONCLUSION

Sixty-six cases of sepsis of the newborn were reviewed from

the records of Grace New Haven Community Hospital. The period covered was from 1957-1963. The predominant infecting organism was E. Coli, which was responsible for 41% of all infections. Klebsiella Aerobacter emerged for the first time in this hospital's records as an important pathogenic organism in neonatal sepsis. With the additional finding of decreased numbers of infections due to gram positive organisms, one is confronted with the fact that the gram negative organisms now make up the majority of pathogens in this disease. Pre-natal factors were felt to be important as a substantial number of mothers had either elevated temperatures the week before delivery or else difficult deliveries. Prematurity was found in one half of the cases and was felt to be one of the main contributing factors to susceptibility to infection. This review showed, and as other investigators have also found, "doing poorly", jaundice and respiratory distress are early indications of sepsis and must always arouse suspicion of this disease. In addition, lethargy, apnea, regurgitation, poor feeding, restlessness and irritability are early clinical signs which were found to be present in a large number of cases and which may, in the future, be important clues for detecting infection early and reliably. The mortality rate in this review was 56% which is comparable to other recent studies.

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